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(54) Title: APPARATUS AND PROCESS FOR PREPARING CRYSTALLINE PARTICLES

(57) Abstract

There is provided according to the present invention a process for preparing crystalline particles, especially particles of a pharmaceutical or carrier substance suitable for inhalation therapy, in addition to an apparatus for the preparation of such particles.

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APPARATUS AND PROCESS FOR PREPARING CRYSTALLINE PARTICLES

This invention relates to a novel apparatus for preparing crystalline particles, particularly particles of defined particle size distribution, especially particles of therapeutically useful or carrier substances of a size suitable for inhalation therapy. There is also provided a process for preparing the same.

Industrial processes for production of many products, particularly pharmaceutical products, require the preparation of pure substances of a defined particle size distribution. Pure substances are frequently prepared by precipitation from solutions of lesser purity. When precipitation takes place relatively slowly (e.g. over a matter of hours), crystals are grown which are frequently of a non-uniform shape and relatively large size.

In the field of inhalation therapy, therapeutic molecules are generally desired of a particle size "suitable for inhalation", which is a term generally taken to indicate an aerodynamic diameter between 1 and 10 μm, especially 1 and 5 μm, particularly 1 and 3 μm. Carrier molecules (such as lactose) for inhaled therapeutic preparations are typically desired of a significantly larger aerodynamic diameter so that they do not penetrate into the upper respiratory tract to the same degree as the active ingredient and an aerodynamic diameter of 100 to 150 μm is generally considered suitable. However this is a generalisation and for some purposes it may well be preferred to use a lower particle size for the carrier, even one comparable to that of the therapeutic substance.

Outside of the inhaled area, modification of the habit and size of crystals is a valuable tool in adjusting and optimising pharmaceutical and biological properties such as flow characteristics, dissolution rate and bioavailability.

Particles of the desired particle size for inhalation therapy are conventionally prepared by milling or micronisation. These processes, depending on the precise conditions adopted, are capable of generating particle distributions which include fractions having particles with the appropriate size. Milling is suitable for preparing particles of the larger size indicated above and

micronisation of the smaller size indicated above. However, there are a number of disadvantages associated with milling and micronisation processes including that the fraction having the desired particle size may be relatively small, that there may be generated a significant fraction of particles that are finer than is desired (which may be deleterious e.g. if it affects bioavailability) and that product losses generally may be considerable (e.g. through coating of the machinery). A further property of micronised products is that the surfaces of the particles generated are generally substantially amorphous (i.e. have minimal crystallinity). This may be undesirable when there exists a tendency for the amorphous regions to convert to a more stable crystalline state. Furthermore micronised or milled products may be more susceptible to moisture uptake than crystalline products. Micronisation and milling processes also suffer from the disadvantages that they are relatively energy intensive and require containment and other measures to avoid the risk of dust explosion.

Rapid precipitation (e.g. by dilution of a solution with an anti-solvent) may give rise to crystalline particles which could be of suitable size, however this technique is notoriously difficult to control and has not found widespread acceptance in the pharmaceutical industry, particularly in relation to inhalation products.

The use of ultrasonic radiation to increase effectiveness of crystallisation in purification of organic substances is described in Yurhevich, *et al.* (1972), Primen. Ul'trazvuka Met. Protsessakh, Mosk. Inst. Stali Splavov **67**, 103-106.

We have now invented a novel process and apparatus for preparing particles which overcomes or substantially mitigates one or more of the above mentioned disadvantages.

Thus according to a first aspect of the invention there is provided a process for preparing crystalline particles of substance which comprises mixing in a continuous flow cell in the presence of ultrasonic radiation a flowing solution of the substance in a liquid solvent with a flowing liquid antisolvent for said substance, and collecting the resultant crystalline particles generated.

A particular advantage of the process is that it is capable of running continuously (subject to adequate supply of solution and anti-solvent) even if, for a particular application, it may be desired to run it only for a relatively short time. Also since the process is an essentially "wet" process it significantly reduces hazards associated with dry particulate matter.

A feature of the process is that in a steady state the concentration of dissolved substance in the mixing chamber of the flow cell remains approximately constant since the precipitating substance is replaced by the inflow of further solution. This allows the process to be run continuously and reproducibly.

We have found that the process according to the invention is capable of being very efficient and economical with product yields of up to 95-98%.

According to a second aspect of the invention there is provided an apparatus for preparing crystalline particles of a substance which comprises
(i) a first reservoir of said substance dissolved in a liquid solvent;
(ii) a second reservoir of liquid antisolvent for said substance;
(iii) a mixing chamber having first and second inlet ports and an outlet port;
(iv) means for delivering the contents of the first and second reservoirs to the mixing chamber via the first and second inlet ports respectively at independent controlled flow rate;
(v) a source of ultrasonic radiation located in the vicinity of the first inlet;
and
(vi) means for collecting crystalline particles suspended in the liquid discharged from the mixing chamber at the outlet port.

According to both the first and second aspects of the invention, preferably the liquid anti-solvent is miscible with the liquid solvent.

Preferably the apparatus further comprises means to mix the liquids delivered to the mixing chamber via the first and second inlets. The preferred means is a stirrer. Most preferably the mixing means should be non grinding e.g. a non-grinding magnetic stirrer or an overhead stirrer (particularly a non-grinding magnetic stirrer).

Desirably, stirring speed will be set at a level that gives efficient mixing in the mixing chamber, but without inducing vortex effects. Vortex effects are undesirable since they have a tendency to disrupt the cavitation caused by the source of ultrasonic radiation. Furthermore they may cause particle size reduction through liquid micronisation-like processes.

Desirably the means for delivering the contents of the first and second reservoirs to the mixing chamber via the first and second inlet ports respectively at independent controlled flow rate comprises one or more pumps. Preferably a pump will be provided for each of the first and second reservoirs. A range of pumps are available and may be suitable for the apparatus according to the invention. The pump may, for example, be a peristaltic pump. Pumps which are essentially non-pulsing are preferred.

The contents of the first and second reservoirs may be delivered to the mixing chamber at a range of flow rates which will be selected and optimised according to the nature of the substance, the solvent, the antisolvent and the power and frequency of the source of ultrasonic radiation. The solubility of the substance in the solvent relative to the anti-solvent is a particularly important variable. The lower this ratio is, the lower may be the flow rate of anti-solvent relative to the substance/solvent solution. Usually the flow rate of the anti-solvent will exceed that of the solvent solution, the excess typically being $\geq$ 2:1 e.g. up to 10:1. Typically flow rates will be in the range of 0.5-100 ml/min especially 0.5-50 ml/min. Higher flow rates of anti-solvent have a tendency to result in crystalline particles of smaller mean size.

Preferably the outlet port of the apparatus is disposed above the inlet ports in the mixing chamber such that the liquid in the mixing chamber flows from a lower to a higher point in the chamber before exiting. This arrangement optimises mixing and allows ready balance of the rates of inflow and outflow.

Preferably the mixing chamber is substantially circular in section and the first and second inlet ports are disposed diametrically opposite each other and at the same height relative to the base of the mixing chamber. Nevertheless, it may be

conceived to orientate the two inlet ports in an off-set manner in order to give some circular motion to the inflowing liquids, although this is not generally preferred.

The position of the outlet port relative to the inlet ports is believed to have an influence on the size of the crystalline particles generated. Without being limited by theory, it is believed that the greater the distance between the inlet ports and outlet port, the greater the average residence time of the particles in the flow cell, the longer the crystalline particles have to mature and hence the larger the mean particle size. However it will be appreciated that mean particle size is subject to a number of other influences.

Preferably the exit port is located approximately half way up the side of the mixing chamber.

In one particular embodiment of the invention, the apparatus according to the invention is provided with a number of optional outlet points at different heights relative to the inlet port. Fractions of differing particles size may then be "tapped" from the different outlet ports.

The mixing chamber may be manufactured from a range of conventional materials however these will preferably be selected so as to be unreactive with the substance, the solvent or the anti-solvent. The mixing chamber may be of any suitable size, whether of a size suitable for bench-scale preparation, industrial pilot scale preparation or industrial manufacturing scale. Substance throughputs are a function of the substance, the concentration and the flow rates. However for the purposes of illustration we have achieved throughputs of certain substances as follows:

Salmeterol xinafoate: Concentration, 0.17g/ml. Flow rate 20ml/min. Output: 204g/hr, 4.9kg/24h.
Fluticasone propionate: Concentration, 0.07g/ml. Flow rate 30ml/min. Output: 126g/hr, 3.0kg/24h.
Salmeterol xinafoate and fluticasone propionate in combination: Concentration, 0.07g/ml. Flow rate 20ml/min. Output: 84g/hr, 2.0kg/24h.

Naratriptan hydrochloride: Concentration, 0.025g/ml. Flow rate 30ml/min. Output: 45g/hr, 1.1kg/24h.

2,6-Diamino-3-(2,3,5-trichlorophenyl)pyrazine: Concentration, 0.07g/ml. Flow rate 33ml/min. Output: 138.6g/hr, 3.33kg/24h.

Particles suspended in the liquid discharged from the mixing chamber at the outlet port may be collected by means of one of a number of conventional particle capturing techniques e.g. filtration or centrifugation. The preferred means is a filtration means; a wide range of suitable filters are known to persons skilled in the art. Examples of filters include sinters (e.g. glass sinters), fibre filters (e.g. paper and nitrocellulose filters) and membrane filters. We have found that a particularly advantageous filtration arrangement involves use of a glass fibre microfilter sandwiched between two Whatman paper filters (e.g. Whatman 54 filters). The particle size of the filter will be appropriate for the product collected. It is possible to modify the distribution of particles at the fine end by selecting a filter size which allows fines to pass through the filter.

In order to reduce the incidence of undesirable "bridging" between particles during harvesting we have found that it is preferable to flush out any residual solvent by thoroughly washing the filter cake with an anti-solvent for the substance. Preferably the anti-solvent will be the same anti-solvent that is used in the main process.

The filter may be provided with a drying facility such as by vacuum and/or heat. In order to facilitate drying especially when the anti-solvent is relatively non-volatile (such as is water) we find that it is advantageous to displace the anti-solvent with a more volatile anti-solvent. Displacement may be achieved by layering the second anti-solvent on top of the filter cake. For many substances, and particularly for salmeterol xinafoate and fluticasone propionate, when the first anti-solvent is water we have found that displacement of the water with diisopropylether (IPE) is particularly satisfactory since approximately 80% of the diisopropylether may be removed by vacuum and remaining 20% by heat at 40 °C. Alternatively the particles of crystalline substance may be collected on a fluidised filter bed and drying achieved with a warm inert gas such as nitrogen gas. Alternatively in a system where the crystallisation of the substance out of

solution is essentially complete, the outflow from the mixing chamber may be fed to a spray-drying facility such that the solvent/antisolvent mixture is vaporised and the particles collected dry.

Generally, before use it may be desirable to sieve the dried product softly through a course sieve to remove soft aggregates without effecting size reduction of the primary particles.

Ultrasound frequencies above around 20kHz are generally suitable; frequencies in the range 20-25kHz are particularly suitable, especially 22kHz. Lower frequencies than these are generally to be avoided since they may fall within a range audible to the human ear. For a given geometry of mixing chamber, certain frequencies may be prone to cancellation. Generally this phenomenon may be avoided by modest tuning of the probe frequency. Ultrasound power in the range 5-5000W may be suitable (although we are not aware of any theoretical upper limit); in general smaller particles are obtainable using higher power.

The source of ultrasonic radiation will be located sufficiently close to the first inlet port such that it efficiently aids induction of precipitation of particles of substance by causing cavitation in the mixing liquids. Preferably the source is located just above the first inlet port. The source preferably includes an ultrasound probe (or perhaps more than one probe). However wrap-around geometries may also be contemplated e.g. wherein ultrasound transducers transmit ultrasonic radiation through pipes. In one such contemplated arrangement the contents of the first and second reservoir are delivered to a Y-shaped junction through inlet arms and one or more ultrasound transducers are attached to the outside of the exit arm. The source of ultrasonic radiation may be enclosed in a protective jacket (e.g. one made of glass) containing a sono-radiation transmission fluid (e.g. silicone or olive oil).

As a further aspect of the invention we provide a process for preparing crystalline particles of a substance using an apparatus according to the invention which comprises

(i) delivering the contents of the first and second reservoirs to the mixing chamber via the first and second inlet ports respectively at independent controlled flow rate;
(ii) supplying ultrasonic radiation to the vicinity of the first inlet;
and
(iii) collecting the crystalline particles suspended in the liquid discharged from the mixing chamber at the outlet port.

The process is particularly suitable for preparing particles of substances which are pharmaceutical or carrier substances suitable for inhalation therapy.

Examples of pharmaceutical substances suitable for inhalation therapy include analgesics, e.g., codeine, dihydromorphine, ergotamine, fentanyl or morphine; anginal preparations, e.g., diltiazem; antiallergics, e.g., cromoglycate, ketotifen or nedocromil; antiinfectives e.g., cephalosporins, penicillins, streptomycin, sulphonamides, tetracyclines and pentamidine; antihistamines, e.g., methapyrilene; anti-inflammatories, e.g., beclomethasone, fluticasone, flunisolide, budesonide, rofleponide, mometasone (e.g. as the furoate) or triamcinolone (e.g. as the acetonide); antitussives, e.g., noscapine; bronchodilators, e.g., albuterol, salmeterol, ephedrine, adrenaline, fenoterol, formoterol (e.g. as the fumarate), isoprenaline, metaproterenol, phenylephrine, phenylpropanolamine, pirbuterol, reproterol, rimiterol, terbutaline, isoetharine, tulobuterol or (-)-4-amino-3,5-dichloro-α-[[[6-[2-(2-pyridinyl)ethoxy] hexyl]methyl] benzenemethanol; diuretics, e.g., amiloride; anticholinergics, e.g., ipratropium (e.g. as the bromide), tiotropium, atropine or oxitropium; hormones, e.g., cortisone, hydrocortisone or prednisolone; xanthines, e.g., aminophylline, choline theophyllinate, lysine theophyllinate or theophylline; therapeutic proteins and peptides, e.g., insulin or glucagon; and salts, esters and solvates of any of the above. Other examples include 4-hydroxy-7-[2-[[2-[[3-(2-phenylethoxy) propyl]sulfonyl]ethyl] amino]ethyl-2(3H)-benzothiazolone and butixicort and salts, esters and solvates thereof.

Examples of other pharmaceutical substances for which the process according to the invention is useful include compounds to be administered orally such as 2(S)-(2-benzoyl-phenylamino)-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-

phenyl}-propionic acid, 2,6-diamino-3-(2,3,5-trichlorophenyl)pyrazine and naratriptan (e.g. as hydrochloride). Pharmaceutical substances as described above include asymmetric molecules which may exist as mixtures of optical isomers (e.g. as racemates) or as purified single enantiomers.

Pharmaceutical substances of particular interest include fluticasone, beclomethasone, salmeterol, salbutamol or an ester, salt or solvate thereof. The substance of most interest is salmeterol xinafoate (including the racemate or the purified r- or s- enantiomers). Fluticasone propionate is also of particular interest.
Examples of carrier substances include lactose.

The solvent and antisolvent liquids will be selected so as to be appropriate for the substance. Preferably, they are readily miscible in the proportions employed. Suitable combinations of solvent/antisolvent include acetone/water, ethanol/IPA, methanol/IPA, methanol/water, DMF/water, DMAc/water, DMSO/water and reciprocal pairs. Methanol/IPE is also a suitable pairing.

1,1,1,2-tetrafluoroethane (HFA134a) and 1,1,1,2,3,3,3-heptafluoro-n-propane (HFA227) are also potential solvents or antisolvents which may be paired e.g. with ethanol. However the use of these gases in liquefied form would require the use of cold or pressurised equipment.

For generation of small particles by the process according to the invention, it is preferred that the difference between the dissolution properties of the solvent and anti-solvent be as great as possible. For reasons of industrial efficiency (particularly in order to reduce the throughput volumes of liquid) it is preferred to use concentrations of substance in solvent which are as high as possible. Nevertheless the solutions must be stable and not prone to crystallisation before discharge into the continuous flow cell. With this end in mind, it may be preferred to use the solution of the substance in the solvent at elevated temperature. It may also be preferable to cool the anti-solvent.

In order to prevent premature precipitation of the dissolved substance in the lines it will generally be desired to prime the apparatus by first pumping it with

solvent. It may be preferred to prime the apparatus by pumping it with heated solvent, particularly when the dissolved substance is close to its solubility limit.

When the substance is fluticasone propionate we prefer the solvent to be acetone and the anti-solvent to be water.

When the substance is salmeterol xinafoate we prefer the solvent to be methanol or acetone (more preferably methanol) and the anti-solvent to be water or IMS (more preferably water).

When the substance is salbutamol sulphate, we prefer the solvent to be water and the anti-solvent to be IMS.

When the substance is beclomethasone dipropionate we prefer the solvent to be IMS and the anti-solvent to be water.

When the substance is lactose we prefer the solvent to be water and the anti-solvent to be ethanol.

When the substance is budesonide, we prefer the solvent to be IMS and the anti-solvent to be water.

When the substance is formoterol fumarate or terbutaline sulphate we prefer the solvent to be methanol or acetone and the anti-solvent to be water or IMS.

When the substance is 2,6-diamino-3-(2,3,5-trichlorophenyl)pyrazine we prefer the solvent to be methanol and the anti-solvent to be water.

When the substance is 2(S)-(2-benzoyl-phenylamino)-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid we prefer the solvent to be acetone and the anti-solvent to be water.

When the substance is naratriptan hydrochloride we prefer the solvent to be methanol and the anti-solvent to be IPE.

We have found that the method according to the invention is suitable for producing populations of mixtures when the substance is a mixture of substances. When the substance is a mixture the method has particular advantages since it is capable of producing mixtures of crystalline particles of very high homogeneity without the need for any blending step. When the substance is a mixture the solvent and anti-solvent will have to be appropriate for all components of the mixture. Differential solubilities in the recrystalline mixture tend to result in the output proportions of the mixture differing from the

initial proportions in solution in the solvent and so appropriate adjustment of the input proportions to achieve the desired output proportions may be necessary.

The method according to the invention is particularly suitable for producing mixtures of crystalline particles of salmeterol and fluticasone or salts and esters thereof e.g. salmeterol xinafoate and fluticasone propionate. The preferred solvent is acetone. The preferred anti-solvent is water. Recrystallisation from acetone using water as anti-solvent tends to cause an increase in the ratio of salmeterol xinafoate to fluticasone propionate relative to their proportion in solution in acetone. The method is also expected to be suitable for producing mixtures of crystalline particles of formoterol and budesonide or salts and esters thereof e.g. formoterol fumarate and budesonide.

As a further aspect of the invention we provide a population of particles obtainable by a process according to the invention.

As one specific aspect of the invention, further elaborated in Example 8, we provide a crystalline particles of 2,6-diamino-3-(2,3,5-trichlorophenyl)pyrazine having a crystal habit in the form of needles as obtainable by a process according to the invention.

Particles of pharmaceutical or carrier substances may be obtained which are suitable for use in a pharmaceutical composition for inhalation therapy, such as dry powder composition (whether containing pure drug, or drug mixed with a carrier such as lactose) or a pressurised liquid formulation (e.g. a formulation comprising a hydrofluoroalkane propellant such as HFA134a or HFA227).

Pressurised liquid formulations suitable for metered-dose inhalers will be retained in canisters, typically aluminium canisters (which may be plastics lined) which are provided with a metering valve of appropriate metering volume.

We also provide a pharmaceutical composition comprising a population of particles prepared according to the invention.

The advantages that the invention may possess include the fact that the process may be performed in a continuous manner without requirements for batch processing, that process may be scaled up with relative ease and that the apparatus and process are capable of producing particle size distributions of very high uniformity index.

The invention will be illustrated by reference to Figure 1 in which mixing chamber 1 is provided with first inlet port 2 connected to first reservoir 3 containing substance dissolved in solvent and second inlet port 4 connected to second reservoir 5 containing anti-solvent. Pumps 6 and 7 deliver liquid from reservoirs 3 and 5 to mixing chamber 1 at a controlled rate. An ultrasound probe 8 is located in the vicinity of, and just above, inlet port 2. When pumps 6 and 7 are in operation, liquids from reservoirs 3 and 5 are delivered to mixing chamber 1 and are mixed with the aid of magnetic stirrer 9. Liquid containing the particles of substance thus generated flows out of the mixing chamber via exit port 10 where they are collected by means of filter 11.

In the mixing chamber used in Examples 1 and 2, the diameter was 5 cm the height was 12.5 cm, the height of the outlet above the base was 7 cm and the height of the inlets above the base was 1.5 cm.

Brief description of the drawings.

Figure 1: Example apparatus according to the invention

Figure 2: Particle size distribution for Run 9 of Example 1

Figures 3-6: Effect graphs as described in Example 1

Figure 7: Particles size distribution for Run 2 of Example 2

Figure 8: Particle size distribution for a standard micronised batch of salmeterol xinafoate

Figures 9-10: Effect graphs as described in Example 2

Figure 11: Particle size distributions for salmeterol xinafoate (micronised batch and Example 3 Run 1)

Figure 12: Particle size distributions for fluticasone propionate (micronised batch and Example 4 Run 1)

Figure 13: Particle size distributions for 6-diamino-3-(2,3,5-trichlorophenyl)pyrazine (batch recrystallised from toluene and Example 8 Runs 2 and 3)

Figure 14: Particle size distributions for naratriptan hydrochloride (micronised batch and Example 9 Run 2)

Abbreviations:

IPA	isopropylalcohol
DMAc	dimethylacetamide
IMS	industrial methylated spirits
DMF	dimethylformamide
IPE	isopropylether
DMSO	dimethylsulphoxide
HFA134a	1,1,1,2-tetrafluoroethane
HFA227	1,1,1,2,3,3,3-heptafluoro-n-propane

Examples

A continuous flow reaction cell with 2 diametrically opposite inlets at the bottom and a run-out ca. half way up the side of the vessel essentially as shown in Figure 1 was used for all experiments. The dimensions of the vessel were: Diameter = 4.4cm; height 12cm. The outlet and inlets were at a height of 6.5cm. There was stirring in all experiments, except where indicated. Except where indicated more precisely, stirring was at a rate adequate to efficiently mix the two incoming streams.

Ultrasound was supplied at a frequency of 22kHz. For Example 1 the ultrasound probe maximum power was 50W and the tables show the power used in each experiment as a percentage of 50W. For Example 2 the ultrasound probe maximum power was 600W and the tables show the power used in each experiment as a percentage of 600W. For the remaining Examples, the ultrasound probe maximum power was 100W and the power used was 100W except where a percentage of maximum which is less than 100 is indicated.

Example 1
Distributions of particles of crystalline fluticasone propionate

Experimental procedure

The drug substance (fluticasone propionate, FP) (8g) is dissolved in acetone (15vol, 0.133M) at elevated temperature (50-56 °C) and then allowed to cool to ambient temperature (20 °C). A solution of FP is then pumped using a peristaltic pump into one of the bottom inlets of the reaction cell. Water was similarly pumped via the other inlet from a water reservoir using a second pump.

Re-crystallisations are carried out from various mixtures of acetone and water (by altering the flow rates of each) as dictated by the parameters set out in the experimental design. Efficient mixing of the two streams is ensured with the aid of a non-grinding magnetic stirrer bar.

Before carrying out any particular crystallisation, the cell is pre-charged with a mixture of acetone/water (the ratio of each being the same as the relative pumping rates from the two reservoirs). By doing this, the relative concentrations of the water to acetone remains constant throughout the crystallisation. The tip of the sono-probe is arranged so that it is just above the inlet for the FP solution. When the magnetic stirrer, sono-probe and pumps are turned on, rapid onset of crystallisation takes place. A suspension of the crystallisation mixture exits via the overflow directly on to a filter funnel thus minimising the opportunity for further crystal growth.

Using the above set-up, the experiments set out in the experimental design shown below were carried out and the samples of damp solid harvested and dried *in vacuo* at ambient temperature. All the samples were sized using the Malvern laser diffraction particle sizer and the results analysed using multi-dimensional model fitting software (such as Design Expert 5).

Experimental Design

Ultrasound, stirring rate using the magnetic stirrer, flow rate of the FP acetone solution and flow rate of the water were included as variables in the

experimental design. Appropriate maximum and minimum values for each of the four variables were chosen as shown in Table 1.

Table 1

Variable	Units	Minimum Value	Mid Point	Maximum Value
A Water antisolvent flow rate	Ml/min	12	18	24
B Drug acetone solution flow rate	Ml/min	3.5	5.25	7.0
C Ultrasound Power	%	0	20	40
D Stirring Rate	%	0	20	40

A half factorial design was chosen to model the 4 variable experiment and the software package Design Expert 5 was used to generate the design. Two centrepoints were added to the design bringing the total number of experiments to 10.

Ultrasound Power is given as a percentage of maximum (50W).

Analysis

Samples were analysed using Malvern laser diffraction particle sizing.

Instrument: Malvern Mastersizer X
Lens: 45mm Reverse Fourier
Analysis: 0607 presentation code
Dispersant: Iso Octane / Lecithin 0.05% w/w
Pre dispersion: Sonicate for 10 seconds
Obscuration: 10% to 16%

One analysis per sample was carried out. The median particle size (D50), particle size at 90% undersize (D90) and particle size at 10% undersize (D10) were used as responses to characterise the medium, course, and fine particles.

In addition a fourth response, uniformity index (UI) was calculated as a measure of the breadth of the distribution.

Results

(a) Size Results

Table 2

Run N°	Water ml/min	Acetone ml/min	Stirring %	U/sound %	D50 (μm)	D10 (μm)	D90 (μm)	UI (%)
1	24	3.50	40.00	0.00	4.95	1.07	18.91	5.7
2	18	5.25	20.00	20.00	4.56	1.02	14.29	7.1
3	24	3.50	0.00	40.00	4.2	1	18.3	5.3
4	12	7.00	0.00	40.00	7.52	2.62	20.83	12.6
5	24	7.00	40.00	40.00	4.3	1.05	14.66	7.2
6	18	5.25	20.00	20.00	5.28	0.89	17.16	5.1
7	12	3.50	0.00	0.00	9.34	2.32	28.97	8
8	12	7.00	40.00	0.00	3.46	1.06	9.33	11.4
9	12	3.50	40.00	40.00	3.67	0.97	11.47	8.5
10	24	7.00	0.00	0.00	9.79	1.48	37.62	3.9

Uniformity Index (UI) is calculated as 100xD10/D90.

The particle size distribution for Run 9 is shown graphically in Figure 2.

(b) Analysis of effects

Effect graphs to show the interdependence of pairs of variables A, B, C, D were constructed using Design Expert 5 and are shown in Figures 3-6.

A- and A+ indicate, respectively, the minimum and maximum values of variable A shown in Table 1. B-/B+, C-/C+ and D-/D+ may be interpreted similarly.

R^2 is a measure of closeness of fit; R^2=1 being the measure of perfect fit.

Figure 3 shows the effect of ultrasound power or stir rate on D50; ultrasound has a major effect and stirring rate has a minor effect (R^2=0.72).

Figure 4 shows the effect of anti-solvent flow rate or ultrasound power on D10; ultrasound and anti-solvent flow rate both have a major effect (R^2=0.94).

Figure 5 shows the effect of ultrasound power or stir rate on D90; Ultrasound has a major effect and stirring rate has a minor effect (R^2=0.72).
Figure 6 shows the effect of anti-solvent flow rate and solvent/drug solution flow rate on UI; flow rate of anti-solvent had a major effect and flow rate of solvent/drug solution had a minor effect (R^2=0.87).

Example 2
Distributions of particles of crystalline salmeterol xinafoate

Experimental procedure
Due to the low solubility of salmeterol xinafoate and hence its propensity to crystallise from solution on cooling, a reservoir containing just pure methanol is heated to reflux and pumped through the system using a peristaltic pump so as to 'warm-up' the lines and associated apparatus. The drug substance (salmeterol xinafoate) (8g) is dissolved in methanol (6vol) at elevated temperature (65 °C). A solution of salmeterol xinafoate (0.276M) is then pumped (a fixed rate of 7ml/min) using a peristaltic pump into one of the bottom inlets of the reaction cell. Cold water was similarly pumped via the other inlet from a water reservoir using a second pump at rates as dictated by the experimental design.

Re-crystallisations are carried out from various mixtures of methanol and water as dictated by the parameters set out in the experimental design. Efficient mixing of the two streams is ensured with the aid of a non-grinding magnetic stirrer bar. The stirrer speed is maintained constant at all times. The stir speed is set at such a rate so as to induce a minimum amount of vortex.

Before carrying out any particular crystallisation, the cell is pre-charged with a mixture of methanol/water (the ratio of each being the same as the relative pumping rates from the two reservoirs). By doing this, the relative concentrations of the water to methanol remains constant throughout the crystallisation. The tip of the sono-probe is arranged so that it is just above the inlet for the salmeterol solution. When the magnetic stirrer, sono-probe and pumps are turned on, rapid onset of crystallisation takes place. A suspension of the crystallisation mixture

exits via the overflow directly on to a filter funnel thus minimising the opportunity for further crystal growth.

Using the above set-up, the experiments set out in the experimental design shown below were carried out and the samples of damp solid harvested and dried *in vacuo* at ambient temperature. All the samples were sized using the Malvern laser diffraction particle sizer and the results analysed using multi-dimensional model fitting software (such as Design Expert 5).

Experimental Design

Ultrasound and flow rate of the water were included as variables in the experimental design. Appropriate maximum and minimum values for each of the two variables were chosen as shown in Table 3.

Table 3

Variable	Units	Minimum Value	Mid Point	Maximum Value
A Water antisolvent flow rate	ml/min	14	35	56
B Ultrasound Power	%	10	50	90

A half factorial design was chosen to model the 2 variable experiment and the software package Design Expert 5 was used to generate the design.

Ultrasound Power is given as a percentage of maximum (600W).

Analysis

Samples were analysed using Malvern laser diffraction particle sizing.

Instrument: Malvern Mastersizer S
Lens: 300mm Reverse Fourier
Analysis: presentation code 30GE
Dispersant: Iso Octane / Lecithin 0.05% w/w
Pre dispersion: Sonicate for 1 Minute
Obscuration: 10% to 20%

One analysis per sample was carried out. The median particle size (D50), particle size at 90% undersize (D90) and particle size at 10% undersize (D10) were used as responses to characterise the medium, course, and fine particles. In addition a fourth response, uniformity index (UI) was calculated as a measure of the breadth of the distribution.

Results

(a) Size Results

Table 4

Run N°	Water ml/min	U/sound %	D50 (μm)	D10 (μm)	D90 (μm)	UI (%)
1	14	10.00	10.1	1.6	24.78	6.46
2	56	10.00	3.9	0.48	10.21	4.70
3	56	90.00	4.24	0.64	14.45	4.42
4	56	90.00	4.29	0.53	17.62	3.01
5	56	10.00	4.74	0.39	16.8	2.32
6	14	10.00	11.09	2.17	23.37	9.28
7	35	50.00	4.75	1.08	13.45	8.03
8	14	90.00	6.37	1.63	20.37	8.00
9	35	50.00	4.99	1.88	11.76	15.99
10	14	90.00	7.86	1.77	24.96	7.09

Uniformity Index (UI) is calculated as 100xD10/D90.

The particle size distribution for Run 2 is shown graphically in Figure 7.

The distribution of a standard micronised batch of salmeterol xinafoate is shown for comparison in Figure 8.

(b) Analysis of effects

Effect graphs to show the interdependence of pairs of variables A and B were constructed using Design Expert 5 and are shown in Figures 9-10.

Figure 9 shows the effect of water anti- solvent flow rate on D50 ("midian p.s."); water anti-solvent flow rate has a major effect.

Figure 10 shows the effect of ultrasound power on D50; ultrasound power has a minor effect.

Example 3

Distributions of particles of crystalline salmeterol xinafoate

Particle distributions of salmeterol xinafoate were prepared essentially as described above for Example 2 except that the salmeterol xinafoate (8g) was dissolved in 6.25 vol of methanol and the methanol and water flow rates used were 20 and 80 ml/min respectively. The particles were collected on a filter formed from a glass fibre microfilter sandwiched between two Whatman 54 filters. After collection the filter cake was washed with water (3x3vol) then IPE (3x3vol), dried at 40 °C under vacuum and sieved through a 250 μm sieve to break up soft aggregates. Yield = 96% (compare: 85-90% typical for micronisation process, depending on scale). Analysis was as for Example 2 except that the pre-dispersion was by shaking instead of sonication. Results (together with a comparison with a typical micronised batch) are shown in Table 5 and Figure11.

Table 5

	D50 (μm)	D10 (μm)	D90 (μm)
Example 3 Run 1	7.16	2.03	24.75
Micronised batch	2.55	1.34	5.09

Amorphous content of Example 3 Run 1 material was below the level of detection by X-ray powder diffraction. Amorphous content of micronisation batch material was estimated at 20-40%.

Example 4

Distributions of particles of crystalline fluticasone propionate

Particle distributions of fluticasone propionate were prepared essentially as described above for Example 1 with flow rates as shown in Table 4. The particles were collected on a filter formed from a glass fibre microfilter

sandwiched between two Whatman 54 filters. After collection the filter cake was washed with water (3x3vol), dried at 40 °C under vacuum and sieved through a 250 μm sieve to break up soft aggregates. Yield = >95% (estimated) (compare: 90-95% typical for micronisation process depending on scale). Analysis was as for Example 2 except that the pre-dispersion was by shaking instead of sonication. Results (together with a comparison with a typical micronised batch) are shown in Table 6 and Figure12.

Table 6

	Flow rate (ml/min) water:acetone	Ultrasound Power (%)	D50 (μm)	D10 (μm)	D90 (μm)
Ex4 Run 1	60:30	100	4.24	1.98	10.16
Ex4 Run 2	60:30	50	4.36	2.01	10.35
Ex4 Run 3	24:6	100	4.16	2.00	15.54
Ex4 Run 4	24:6	50	4.64	2.02	11.26
Micronised batch			4.66	1.88	18.43

Amorphous content of Example 4 Runs1-4 material was below the level of detection by X-ray powder diffraction. Amorphous content of micronisation batch material was estimated at 20-40%.

Ultrasound Power is given a percentage of maximum (100W).

Example 5

Distributions of a mixture of particles of crystalline fluticasone propionate and crystalline salmeterol xinafoate

Salmeterol xinafoate and fluticasone propionate (5.5g of a 1:10 w/w mix) were dissolved in acetone (15 vol). Water was used as anti-solvent. Drug/acetone and water flow rates were 20ml/min and 80 ml/min respectively. The particles were collected on a filter formed from a glass fibre microfilter sandwiched between two Whatman 54 filters. After collection the filter cake was washed

with water (3x3vol) then IPE (3x3vol), dried at 40 °C under vacuum and sieved through a 250 μm sieve to break up soft aggregates. Yield = 94%; ratio of salmeterol xinafoate to fluticasone propionate in recovered product was 1:13 (by ^{1}H nmr). Analysis was as for Example 2 except that the pre-dispersion was by shaking instead of sonication. Results are shown in Table 7.

Table 7

	D50 (μm)	D10 (μm)	D90 (μm)
Example 5 Run 1	6.38	2.06	44.39

Example 6

An aluminium canister may be charged with particles of (a) fluticasone propionate or (b) salmeterol xinafoate or prepared according to the invention (e.g. as described in Examples 1,4 or 2,3 respectively). A metering valve (Valois) may be crimped on and liquefied HFA134a added through the valve.

An aluminium canister may be charged with particles of mixture of fluticasone propionate and salmeterol xinafoate prepared according to the invention (e.g. as described in Example 5). A metering valve (Valois) may be crimped on and liquefied HFA134a added through the valve.

Example 7

A dry powder composition for inhalation may be prepared by mixing particles of (a) fluticasone propionate or (b) salmeterol xinafoate prepared according to the invention (e.g. as described in Examples 1,4 or 2,3 respectively) with milled lactose.

A dry powder composition for inhalation may be prepared by mixing particles of a mixture of fluticasone propionate and salmeterol xinafoate prepared according to the invention (e.g. as described in Example 5) with milled lactose.

Example 8

Distributions of particles of crystalline 2,6-diamino-3-(2,3,5-trichlorophenyl)pyrazine

The product of Example 1 of WO98/38174 (5g) was dissolved in methanol (15 vol). Water was used as anti-solvent. The particles were collected on a filter formed from a glass fibre microfilter sandwiched between two Whatman 54 filters. After collection the filter cake was washed with water (3x3vol) then IPE (3x3vol), dried at 40 °C under vacuum and sieved through a 250 μm sieve to break up soft aggregates. Analysis was as for Example 2 except that the pre-dispersion was by shaking instead of sonication. Results are shown in Table 8 and Figure 13. Material obtained from Example 9 runs 1 to 4 appeared under scanning electron microscopy as matted needles consisting of soft aggregates, size <<4 μm. A comparison is given with material obtained by recrystallising the compound from toluene in a conventional manner. This material appeared under scanning electron microscopy as tablet like crystals, size ca. 150-500 μm. Since the peak positions in the diffraction pattern from X-ray powder diffraction was essentially the same for these two materials, although the peak intensities were different, this suggests that a novel crystal habit of the same polymorph has been generated by the process according to the invention.

Table 8

	Flow rate (ml/min) Water:methanol	D50 (μm)	D10 (μm)	D90 (μm)
Ex8 Run 1	24:6	2.97	0.29	12.01
Ex8 Run 2	66:33	3.54	0.24	24.16
Ex8 Run 3	24:6	1.64	0.22	10.30
Ex8 Run 4	60:30	3.18	0.23	30.27
Batch recrystallised from toluene		441.94	199.40	692.13

Distributions of particles of crystalline 2,6-diamino-3-(2,3,5-trichlorophenyl)pyrazine may be used in the preparation of tablets suitable for the treatment of epilepsy or bipolar disorder.

Example 9

Distributions of particles of crystalline naratriptan hydrochloride

Naratriptan hydrochloride (5g) was dissolved in hot methanol (40.6vol). IPE was used as anti-solvent. The particles were collected on a filter formed from a glass fibre microfilter sandwiched between two Whatman 54 filters. After collection the filter cake was washed with IPE (3x3vol), dried at 40 °C under vacuum and sieved through a 250 μm sieve to break up soft aggregates Yield: 79% approx. Analysis was as for Example 2 except that the pre-dispersion was by shaking instead of sonication. Results are shown in Table 9 and Figure 14. A comparison is shown with a micronised batch.

Table 9

	Flow rate (ml/min) IPE:methanol	D50 (μm)	D10 (μm)	D90 (μm)
Ex9 Run 1	80:20	13.87	2.31	93.81
Ex9 Run 2	60:30	11.90	2.51	69.37
Ex9 Run 3	24:6	6.83	1.20	37.85
Micronised batch		42.60	11.64	109.17

The large D90 figure is attributed to failure to break down large aggregates on sieving. Distributions of particles of crystalline naratriptan hydrochloride may be used in the preparation of tablets suitable for the treatment of migraine.

Claims

1. A process for preparing crystalline particles of substance which comprises mixing in a continuous flow cell in the presence of ultrasonic radiation a flowing solution of the substance in a liquid solvent with a flowing liquid antisolvent for said substance, and collecting the resultant crystalline particles generated.

2. An apparatus for preparing crystalline particles of a substance which comprises

(i) a first reservoir of said substance dissolved in a liquid solvent;

(ii) a second reservoir of liquid antisolvent for said substance;

(iii) a mixing chamber having first and second inlet ports and an outlet port;

(iv) means for delivering the contents of the first and second reservoirs to the mixing chamber via the first and second inlet ports respectively at independent controlled flow rate;

(v) a source of ultrasonic radiation located in the vicinity of the first inlet;

and

(vi) means for collecting particles suspended in the liquid discharged from the mixing chamber at the outlet port.

3. A process according to claim 1 wherein the liquid antisolvent is miscible with the liquid solvent.

4. An apparatus according to claim 2 wherein the liquid antisolvent is miscible with the liquid solvent.

5. An apparatus according to claim 2 or 4 further comprising means to mix the liquids delivered to the mixing chamber via the first and second inlets.

6. An apparatus according to claim 3 or 5 wherein the mixing means comprises a stirrer.

7. An apparatus according to claim 2 or 4 wherein the means for delivering the contents of the first and second reservoirs to the mixing chamber via the first and second inlet ports respectively at independent controlled flow rate comprises one or more pumps;

8. An apparatus according to claim 2 or 4 wherein the outlet port is disposed above the inlet ports in the mixing chamber such that the liquid in the mixing chamber flows from a lower to a higher point in the chamber before exiting.

9. An apparatus according to claim 2 or 4 wherein the mixing chamber is substantially circular in section and the first and second inlet ports are disposed diametrically opposite each other and at the same height relative to the base of the mixing chamber.

10. An apparatus according to claim 2 or 4 wherein the means for collecting particles suspended in the liquid discharged from the mixing chamber at the outlet port comprises a filter.

11. A process according to claim 1 or 3 using an apparatus according to claim 2 or 4 which comprises

(i) delivering the contents of the first and second reservoirs to the mixing chamber via the first and second inlet ports respectively at independent controlled flow rate;

(ii) supplying ultrasonic radiation to the vicinity of the first inlet; and

(iii) collecting the crystalline particles suspended in the liquid discharged from the mixing chamber at the outlet port.

12. A process according to claim 11 wherein the substance is a pharmaceutical or carrier substance suitable for inhalation therapy.

13. A process according to claim 12 wherein the substance is fluticasone, beclomethasone, salmeterol, salbutamol or an ester, salt or solvate thereof.

14. A process according to claim 12 wherein the substance is lactose.

15. A process according to claim 13 wherein the substance is fluticasone propionate.

16. A process according to claim 13 wherein the substance is salmeterol xinafoate.

17. A process according to any one of claims 1, 3, 11 or 12 wherein the substance is a mixture.

18. A process according to claim 17 wherein the substance is a mixture of fluticasone propionate and salmeterol xinafoate.

19. A process according to claim 15 or claim 18 wherein the solvent is acetone and the anti-solvent is water.

20. A process according to claim 16 wherein the solvent is methanol and the anti-solvent is water.

21. A process according to claim 11 wherein the substance is 2,6-diamino-3-(2,3,5-trichlorophenyl)pyrazine.

22. A process according to claim 11 wherein the substance is 2(S)-(2-benzoyl-phenylamino)-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid.

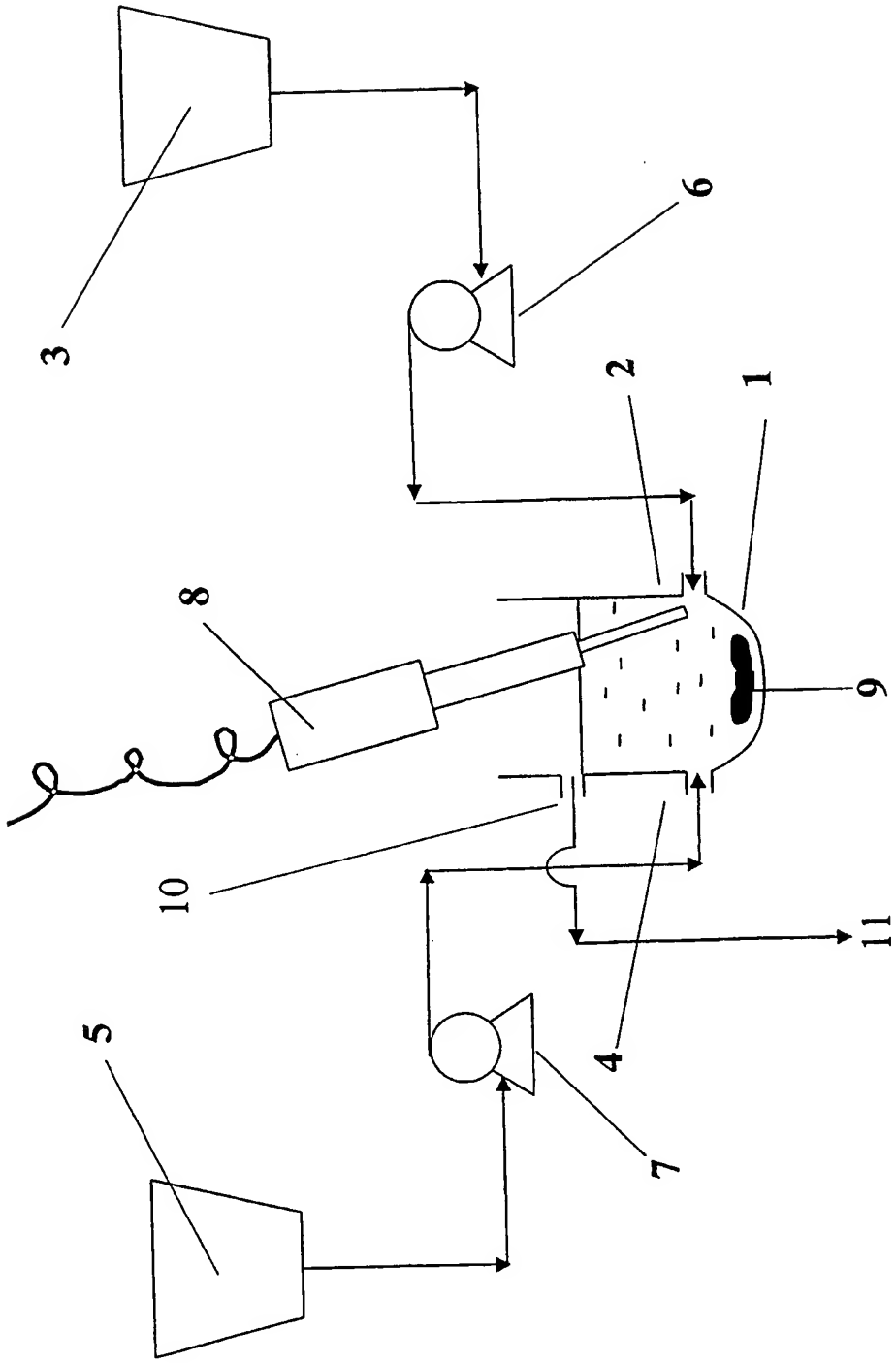
23. A process according to claim 11 wherein the substance is naratriptan hydrochloride.

24. A population of particles obtainable by a process according to any one of claims 1, 3 or 11 to 23.

25. A pharmaceutical composition comprising a population of particles according to claim 24.

26. Crystalline particles of 2,6-diamino-3-(2,3,5-trichlorophenyl)pyrazine having a crystal habit in the form of needles as obtainable by a process according to claim 1.

FIG.1



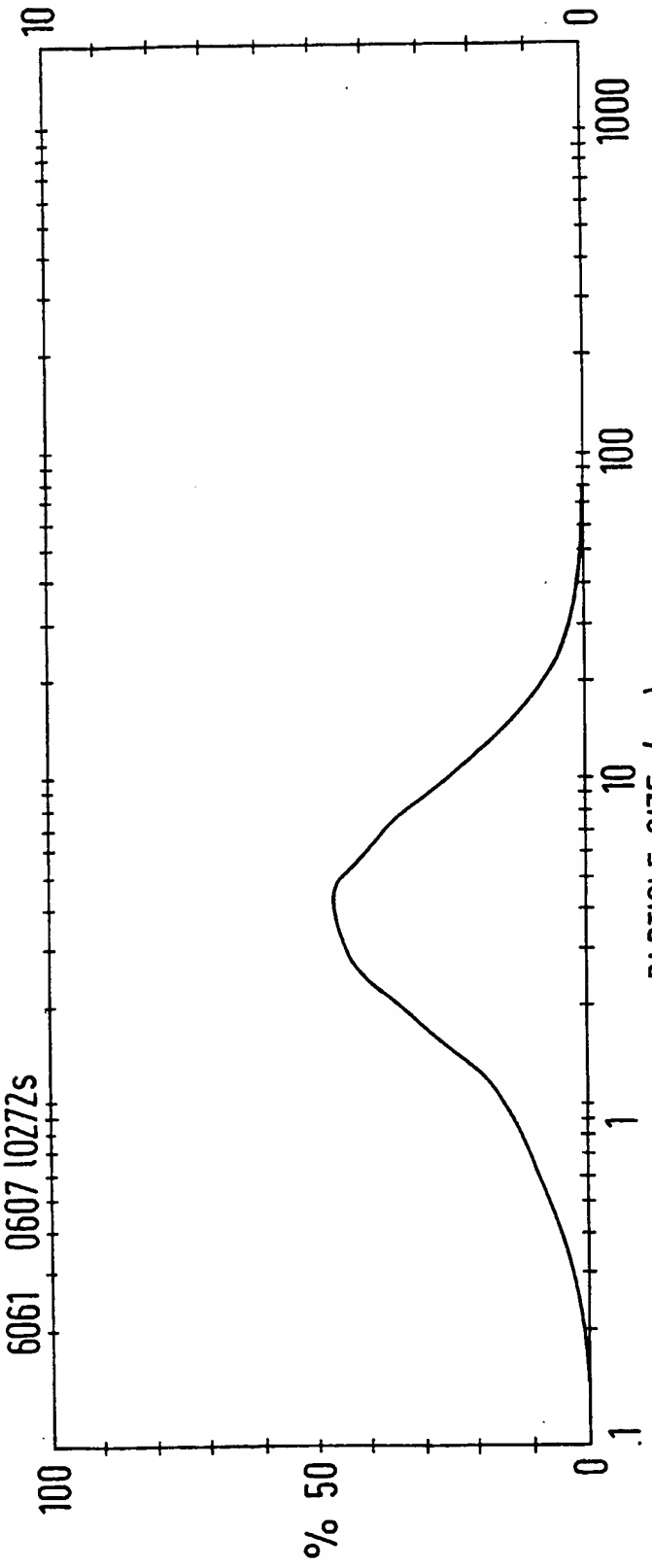


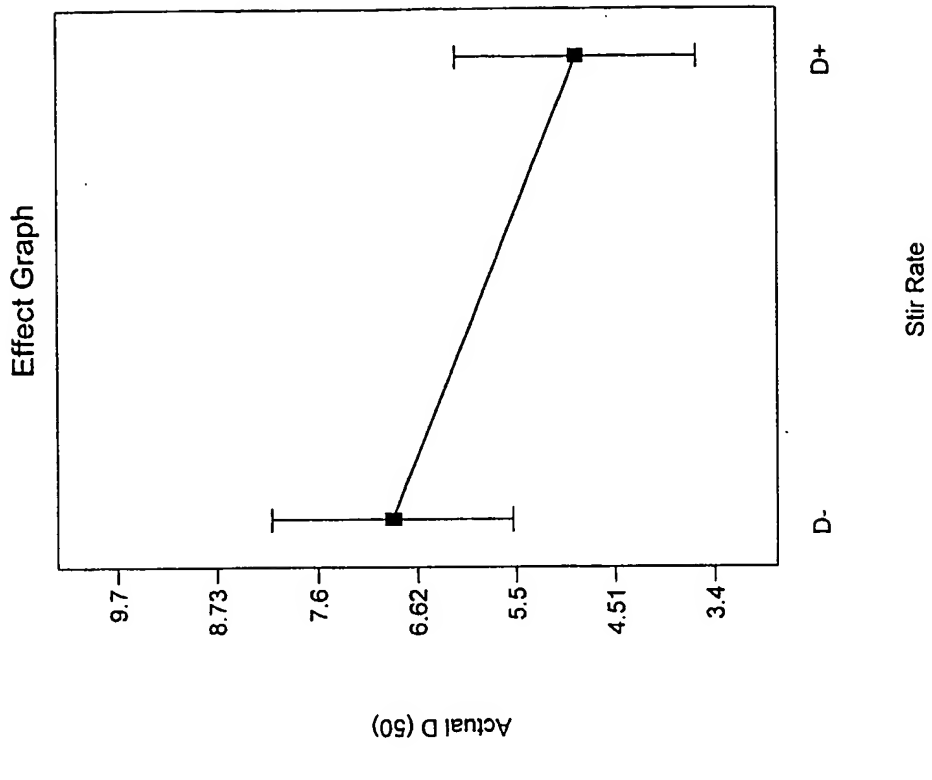
FIG.2A

High Size	Under %	High Size	Under %	High Size	Under %	High Size	Under %	High Size	Under %	High Size	Under %	Span 2.86
80.0	100	24.9	98.3	7.75	79.9	2.41	32.6	0.75	6.9	0.23	0.6	D[4,3] 5.45μm
71.9	100	22.4	97.8	6.97	76.3	2.17	28.8	0.68	5.8	0.21	0.4	
64.7	99.9	20.1	97.2	6.27	72.5	1.95	25.3	0.61	4.8	0.19	0.3	
58.2	99.9	18.1	96.4	5.64	68.4	1.75	22.1	0.55	4.0	0.17	0.2	D[3,2] 2.08μm
52.3	99.8	16.3	95.3	5.07	64.1	1.58	19.2	0.49	3.2	0.15	0.1	
47.1	99.7	14.6	94.0	4.56	59.5	1.42	16.6	0.44	2.6	0.14	0.1	
42.3	99.6	13.2	92.5	4.10	54.9	1.28	14.4	0.40	2.1	0.12	0.1	D[v,0.9] 11.47μm
38.1	99.4	11.8	90.6	3.69	50.2	1.15	12.5	0.36	1.6	0.11	0.0	
34.2	99.3	10.7	88.5	3.32	45.7	1.03	10.9	0.32	1.3	0.10	0.0	
30.8	99.0	9.58	85.9	2.98	41.2	0.93	9.4	0.29	1.0			D[v,0.1] 0.97μm
27.7	98.7	8.62	83.1	2.68	36.8	0.83	8.1	0.26	0.7			
Source = Data:19aug98 Record No. = 11 Focal length = 45 mm Presentation = 0607				Beam length = 2.4 mm Residual = 0.378 % Obscuration = 0.1470 Volume distribution				Model indp Volume Conc. = 0.0059% Sp.S.A 2.8848 m²/cc.				D[v,0.5] 3.67μm Shape OFF

MALVERN INSTRUMENTS

FIG.2B

FIG.3


Effect Graph
Actual D (50)
9.7
8.73
7.6
6.62
5.5
4.51
3.4
D-
D+
Stir Rate

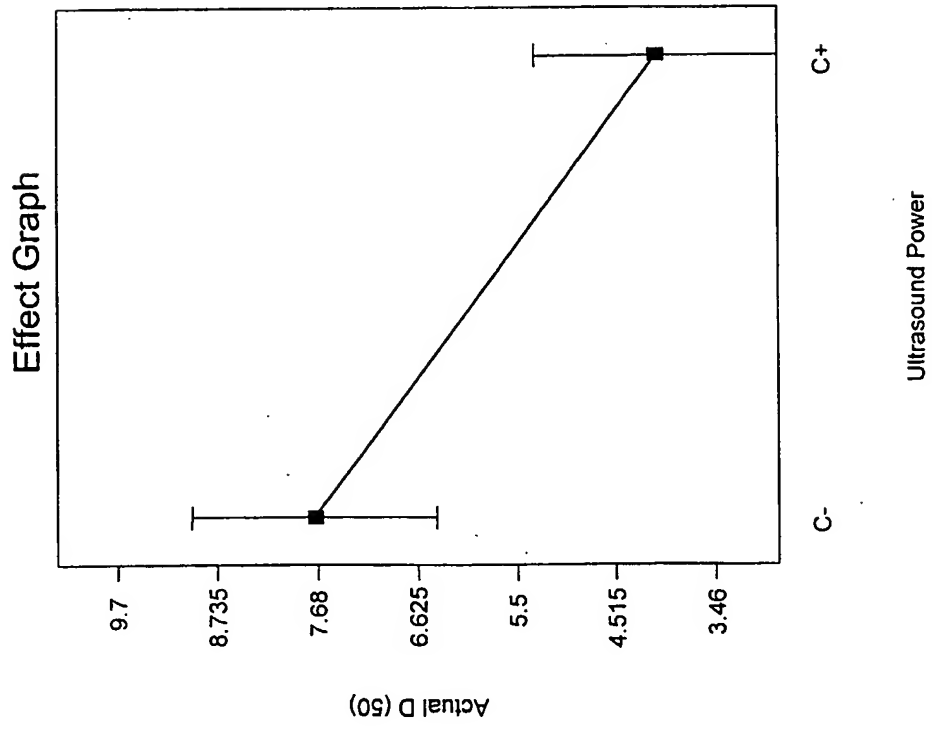

Effect Graph
Actual D (50)
9.7
8.735
7.68
6.625
5.5
4.515
3.46
C-
C+
Ultrasound Power

FIG.4

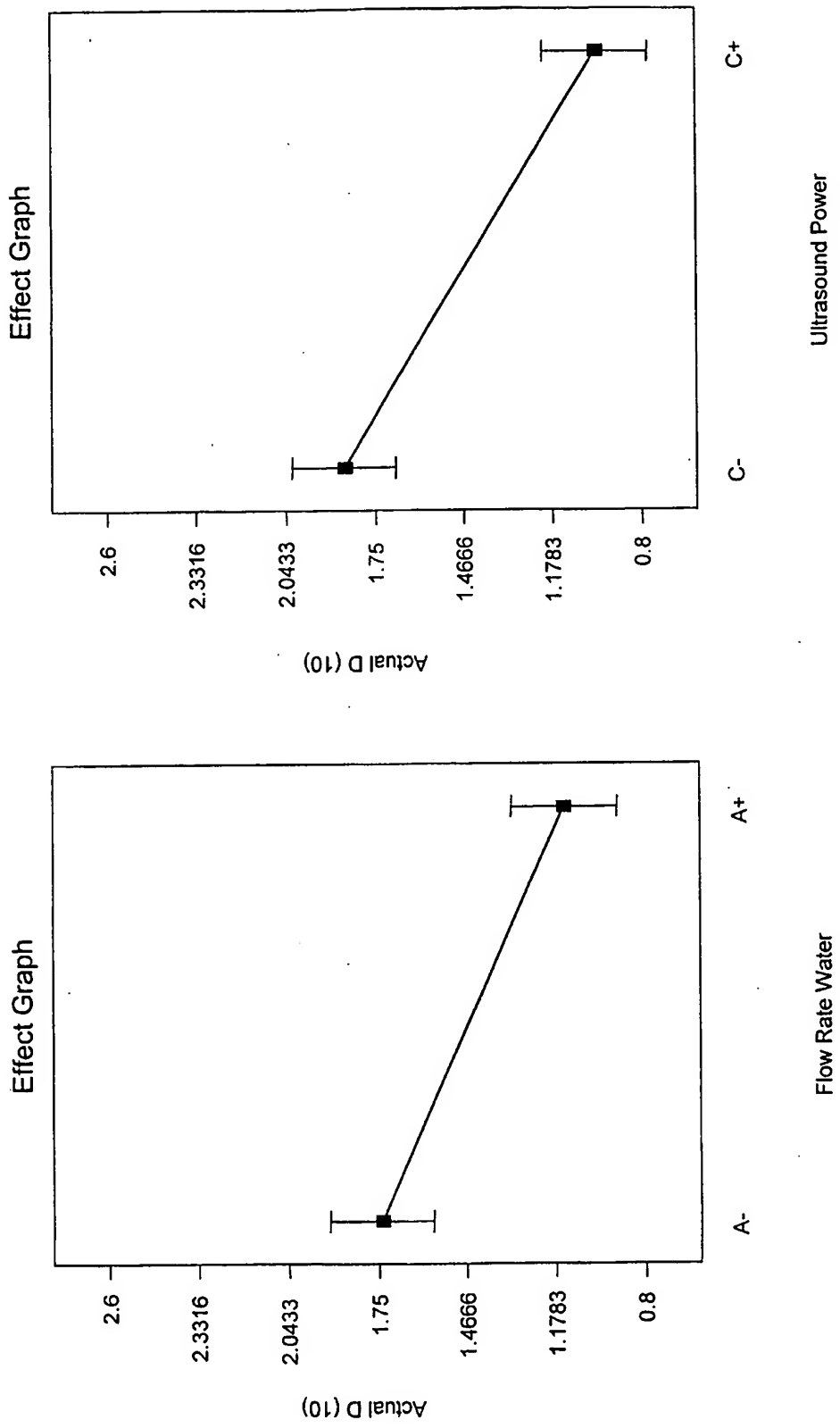
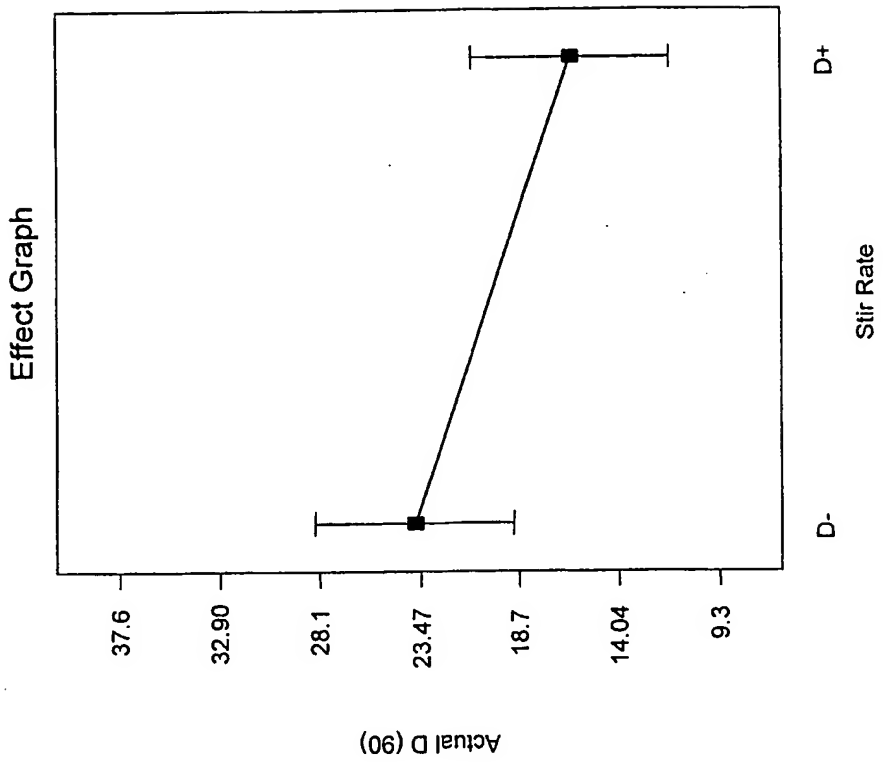

Effect Graph
Actual D (10)
2.6
2.3316
2.0433
1.75
1.4666
1.1783
0.8
C-
C+
Ultrasound Power
Effect Graph
Actual D (10)
2.6
2.3316
2.0433
1.75
1.4666
1.1783
0.8
A-
A+
Flow Rate Water

FIG.5


Effect Graph
Actual D (90)
37.6
32.90
28.1
23.47
18.7
14.04
9.3
D-
D+
Stir Rate

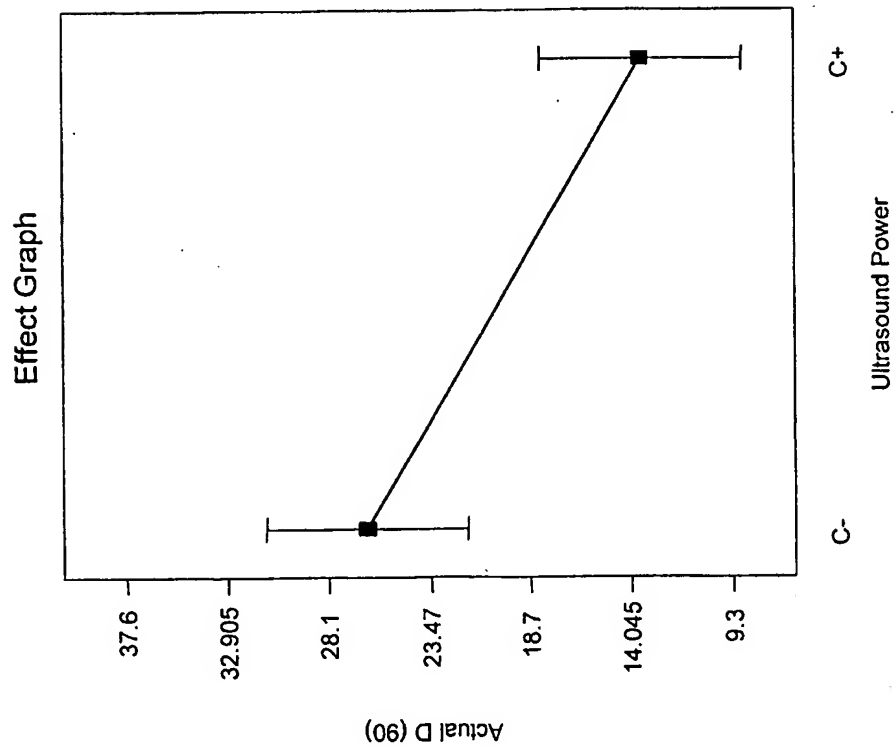
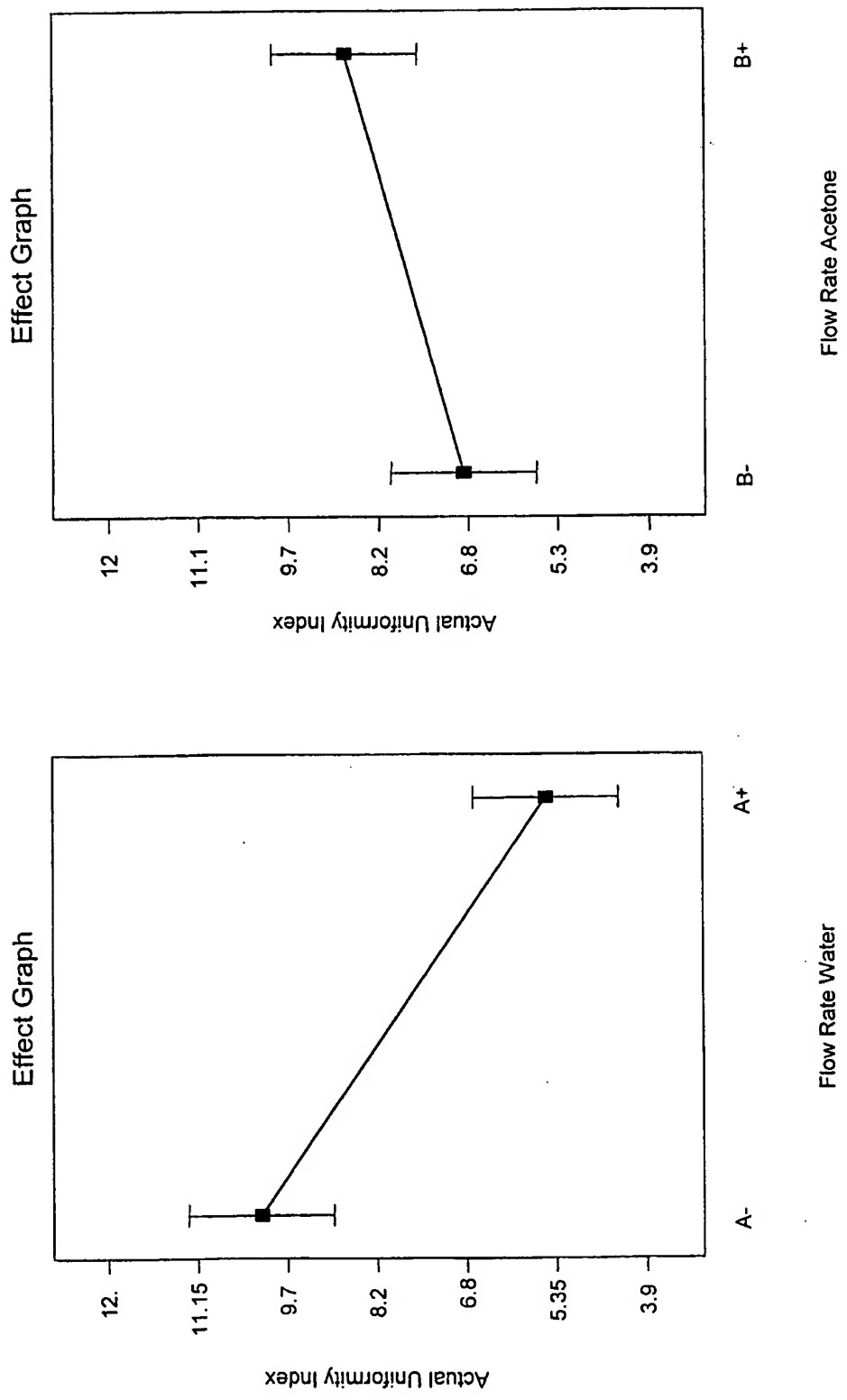

Effect Graph
Actual D (90)
37.6
32.905
28.1
23.47
18.7
14.045
9.3
C-
C+
Ultrasound Power

FIG.6


Effect Graph
Actual Uniformity Index
12.
11.15
9.7
8.2
6.8
5.35
3.9
A-
A+
Flow Rate Water
Effect Graph
Actual Uniformity Index
12
11.1
9.7
8.2
6.8
5.3
3.9
B-
B+
Flow Rate Acetone

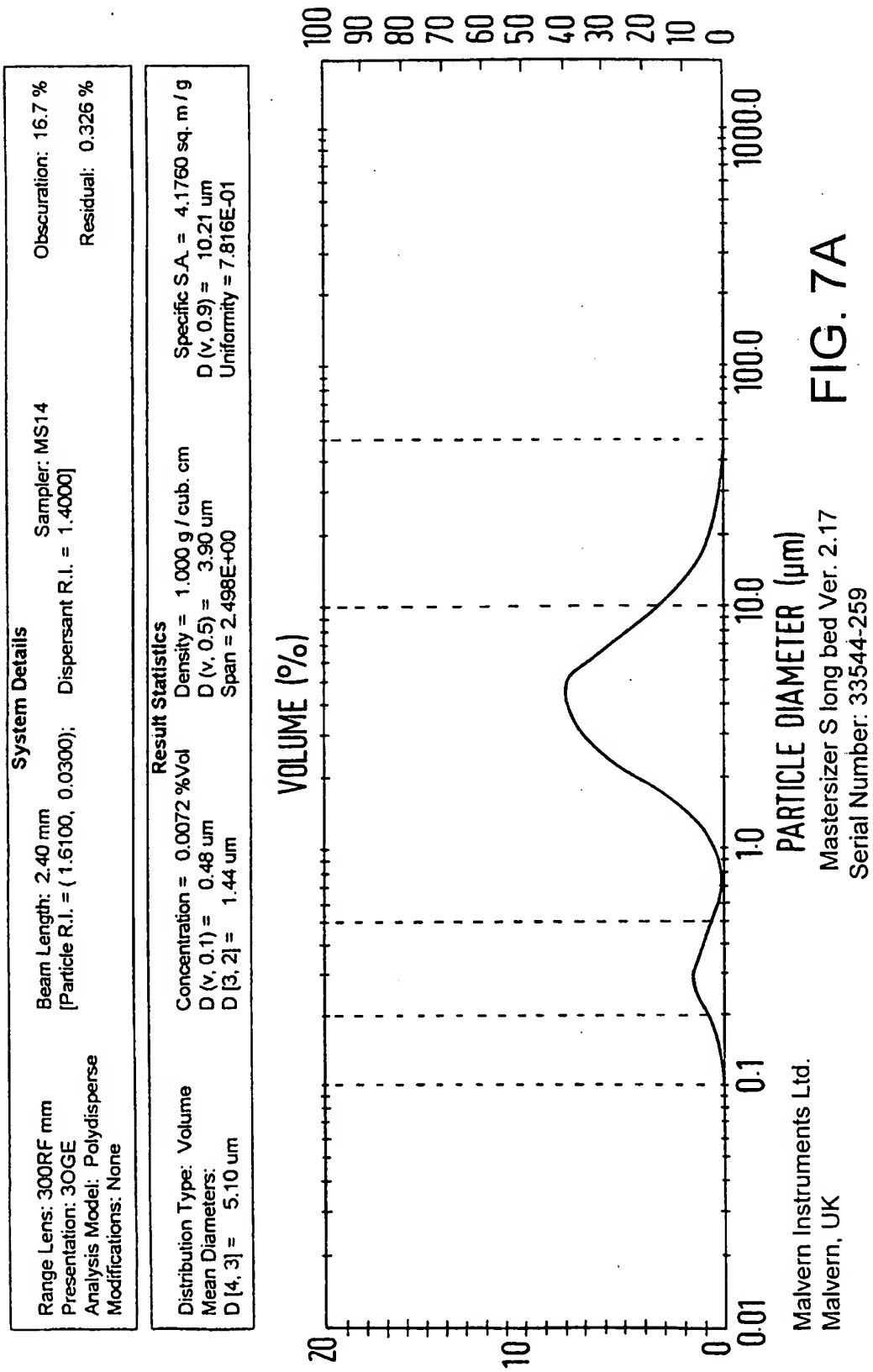

System Details
Range Lens: 300RF mm
Presentation: 3OGE
Analysis Model: Polydisperse
Modifications: None
Beam Length: 2.40 mm
[Particle R.I. = (1.6100, 0.0300);
Dispersant R.I. = 1.4000]
Sampler: MS14
Obscuration: 16.7 %
Residual: 0.326 %
Result Statistics
Distribution Type: Volume
Mean Diameters:
D [4, 3] = 5.10 um
Concentration = 0.0072 %Vol
D (v, 0.1) = 0.48 um
D [3, 2] = 1.44 um
Density = 1.000 g / cub. cm
D (v, 0.5) = 3.90 um
Span = 2.498E+00
Specific S.A. = 4.1760 sq. m / g
D (v, 0.9) = 10.21 um
Uniformity = 7.816E-01
VOLUME (%)
PARTICLE DIAMETER (µm)
Malvern Instruments Ltd.
Malvern, UK
Mastersizer S long bed Ver. 2.17
Serial Number: 33544-259

FIG. 7A

Size (um)	Volume In %
0.055	0.01
0.061	0.05
0.074	0.05
0.082	0.06
0.090	0.09
0.100	0.10
0.109	0.14
0.120	0.19
0.133	0.25
0.147	0.31
0.162	0.39
0.178	0.65
0.200	0.58
0.217	0.82
0.239	0.95
0.263	1.41
0.300	0.68
0.320	0.96
0.353	0.84
0.389	0.22
0.400	1.15
0.474	0.30
0.500	0.62
0.576	0.13
0.600	0.32

Size (um)	Volume In %
0.700	0.13
0.772	0.19
0.851	0.27
0.938	0.23
1.00	0.64
1.14	0.72
1.26	0.98
1.39	1.29
1.53	1.75
1.69	2.11
1.86	1.91
2.00	3.87
2.26	3.63
2.49	4.16
2.75	4.40
3.03	4.66
3.34	4.98
3.69	5.06
4.07	5.00
4.48	5.73
5.00	4.43
5.45	4.72
6.01	4.30
6.63	3.84
7.31	3.38
8.06	

Size (um)	Volume In %
8.06	2.93
8.89	2.48
9.80	0.46
10.00	3.33
11.91	1.42
13.14	1.15
14.49	0.93
15.97	0.77
17.62	0.79
20.00	0.35
21.42	0.43
23.62	0.36
26.04	0.29
28.72	0.11
30.00	0.31
34.92	0.12
38.50	0.04
40.00	0.04
42.45	0.02
50.00	0.00
56.92	0.00
62.76	0.00
69.21	0.00
76.32	0.00
84.15	0.00
92.79	0.00

Size (um)	Volume In %
92.79	0.00
100.00	0.00
112.8	0.00
124.4	0.00
150.0	0.00
151.3	0.00
166.8	0.00
183.9	0.00
200.0	0.00
223.6	0.00
250.0	0.00
271.9	0.00
300.0	0.00
330.6	0.00
364.6	0.00
400.0	0.00
443.3	0.00
488.8	0.00
500.0	0.00
600.0	0.00
651.4	0.00
655.4	0.00
700.0	0.00
800.0	0.00
850.0	0.00
878.7	0.00

FIG. 7B

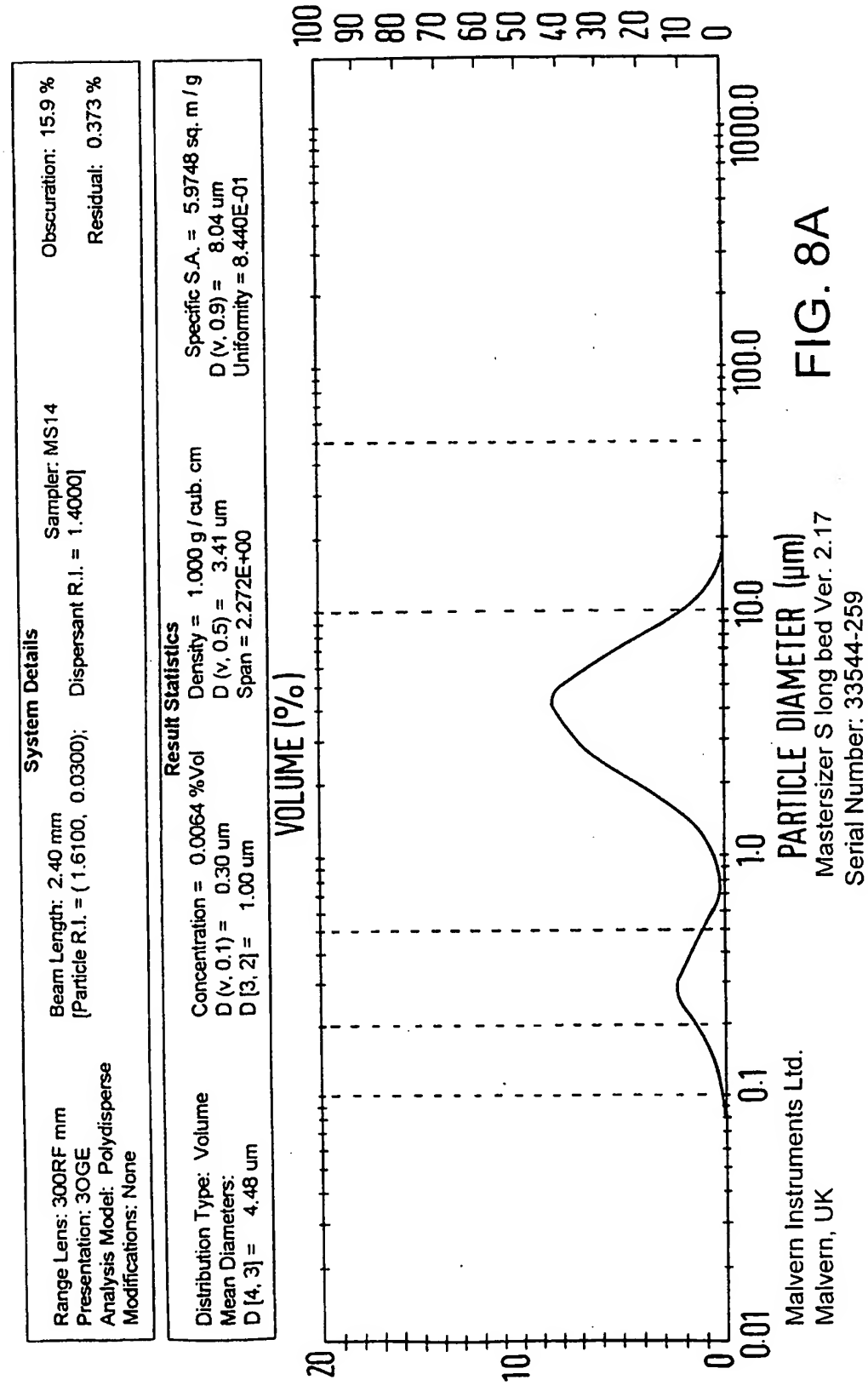

System Details
Range Lens: 300RF mm
Beam Length: 2.40 mm
Sampler: MS14
Obscuration: 15.9 %
Presentation: 3OGE
[Particle R.I. = (1.6100, 0.0300); Dispersant R.I. = 1.4000]
Residual: 0.373 %
Analysis Model: Polydisperse
Modifications: None
Result Statistics
Distribution Type: Volume
Concentration = 0.0064 %Vol
Density = 1.000 g / cub. cm
Specific S.A. = 5.9748 sq. m / g
Mean Diameters:
D (v, 0.1) = 0.30 um
D (v, 0.5) = 3.41 um
D (v, 0.9) = 8.04 um
D [4, 3] = 4.48 um
D [3, 2] = 1.00 um
Span = 2.272E+00
Uniformity = 8.440E-01
VOLUME (%)
PARTICLE DIAMETER (µm)
Malvern Instruments Ltd.
Malvern, UK
Mastersizer S long bed Ver. 2.17
Serial Number: 33544-259

FIG. 8A

Size (um)	Volume In %
0.055	0.04
0.061	0.14
0.074	0.12
0.082	0.13
0.090	0.19
0.100	0.20
0.109	0.27
0.120	0.37
0.133	0.45
0.147	0.55
0.162	0.67
0.178	1.07
0.200	0.92
0.217	1.29
0.239	1.46
0.263	2.14
0.300	1.03
0.320	1.46
0.353	1.28
0.389	0.34
0.400	1.79
0.474	0.47
0.500	0.98
0.576	0.21
0.600	0.54

Size (um)	Volume In %
0.700	0.20
0.772	0.23
0.851	0.29
0.938	0.22
1.00	0.61
1.14	0.68
1.26	0.93
1.39	1.23
1.53	1.68
1.69	2.05
1.86	1.88
2.00	3.83
2.26	3.62
2.49	4.19
2.75	4.47
3.03	4.78
3.34	5.13
3.69	5.25
4.07	5.34
4.48	6.04
5.00	4.39
5.45	4.55
6.01	4.05
6.63	3.45
7.31	2.87
8.06	

Size (um)	Volume In %
8.06	2.31
8.89	1.77
9.80	0.31
10.00	1.91
11.91	0.61
13.14	0.38
14.49	0.23
15.97	0.14
17.62	0.15
20.00	0.10
21.42	0.18
23.62	0.20
26.04	0.23
28.72	0.11
30.00	0.37
34.92	0.22
38.50	0.08
40.00	0.11
42.45	0.24
50.00	0.12
56.92	0.06
62.76	0.04
69.21	0.02
76.32	0.01
84.15	0.01
92.79	

Size (um)	Volume In %
92.79	0.01
100.00	0.01
112.8	0.01
124.4	0.01
150.0	0.00
151.3	0.00
166.8	0.00
183.9	0.00
200.0	0.00
223.6	0.00
250.0	0.00
271.9	0.00
300.0	0.00
330.6	0.00
364.6	0.00
400.0	0.00
443.3	0.00
488.8	0.00
500.0	0.00
600.0	0.00
651.4	0.00
655.4	0.00
700.0	0.00
800.0	0.00
850.0	0.00
878.7	0.00

FIG. 8B

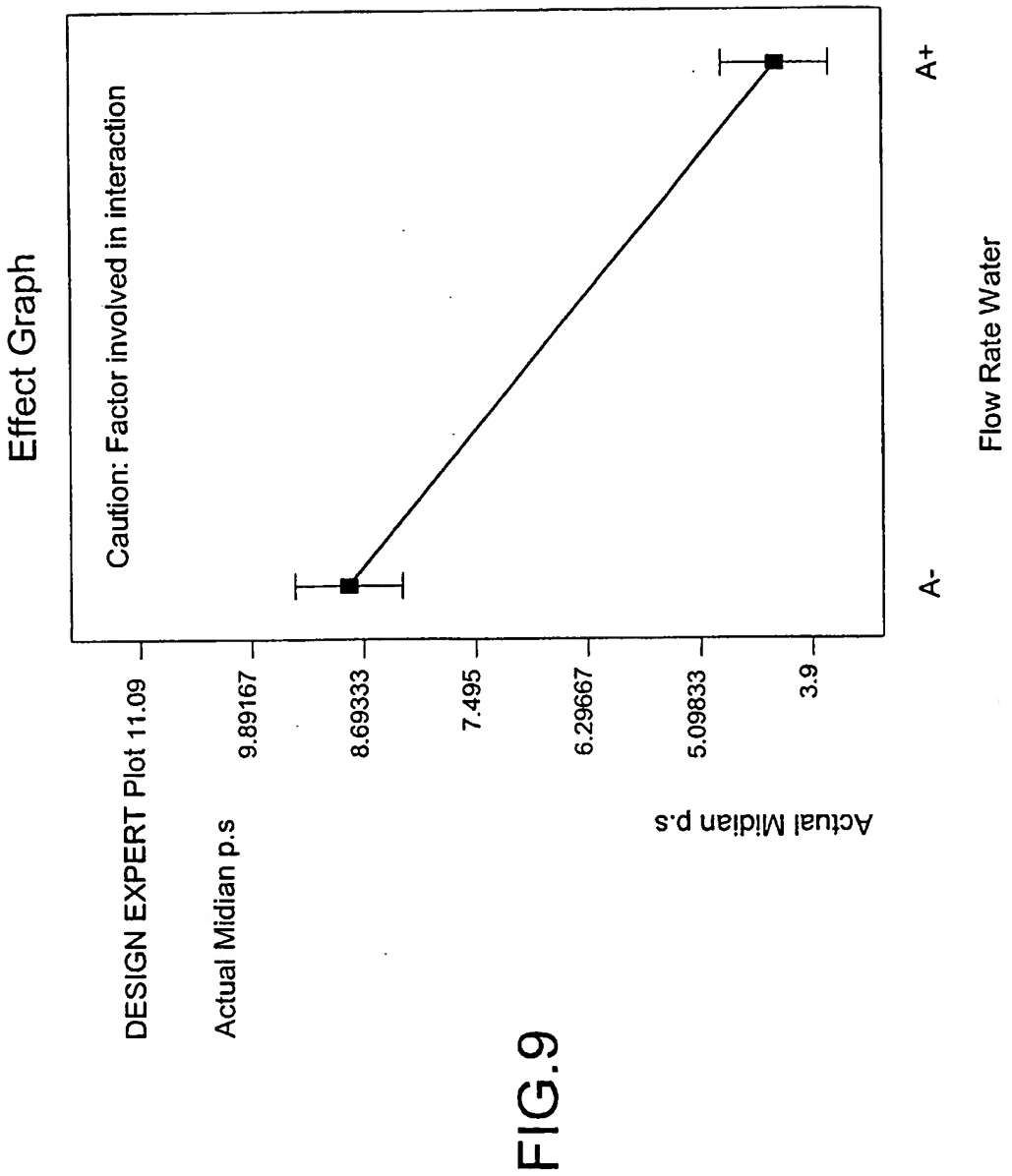

Effect Graph
Caution: Factor involved in interaction
DESIGN EXPERT Plot 11.09
Actual Midian p.s
9.89167
8.69333
7.495
6.29667
5.09833
3.9
Actual Midian p.s
A-
A+
Flow Rate Water

FIG.9

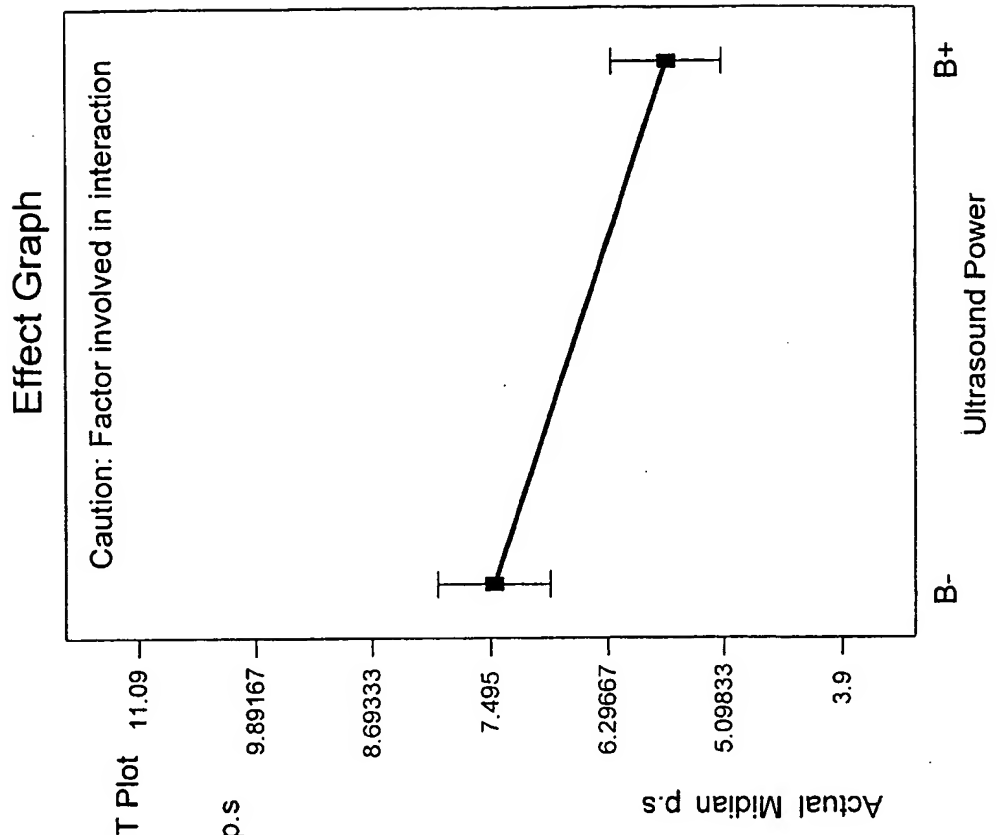

Effect Graph
Caution: Factor involved in interaction
DESIGN EXPERT Plot
Actual Midian p.s
11.09
9.89167
8.69333
7.495
6.29667
5.09833
3.9
Actual Midian p.s
B-
B+
Ultrasound Power

FIG.10

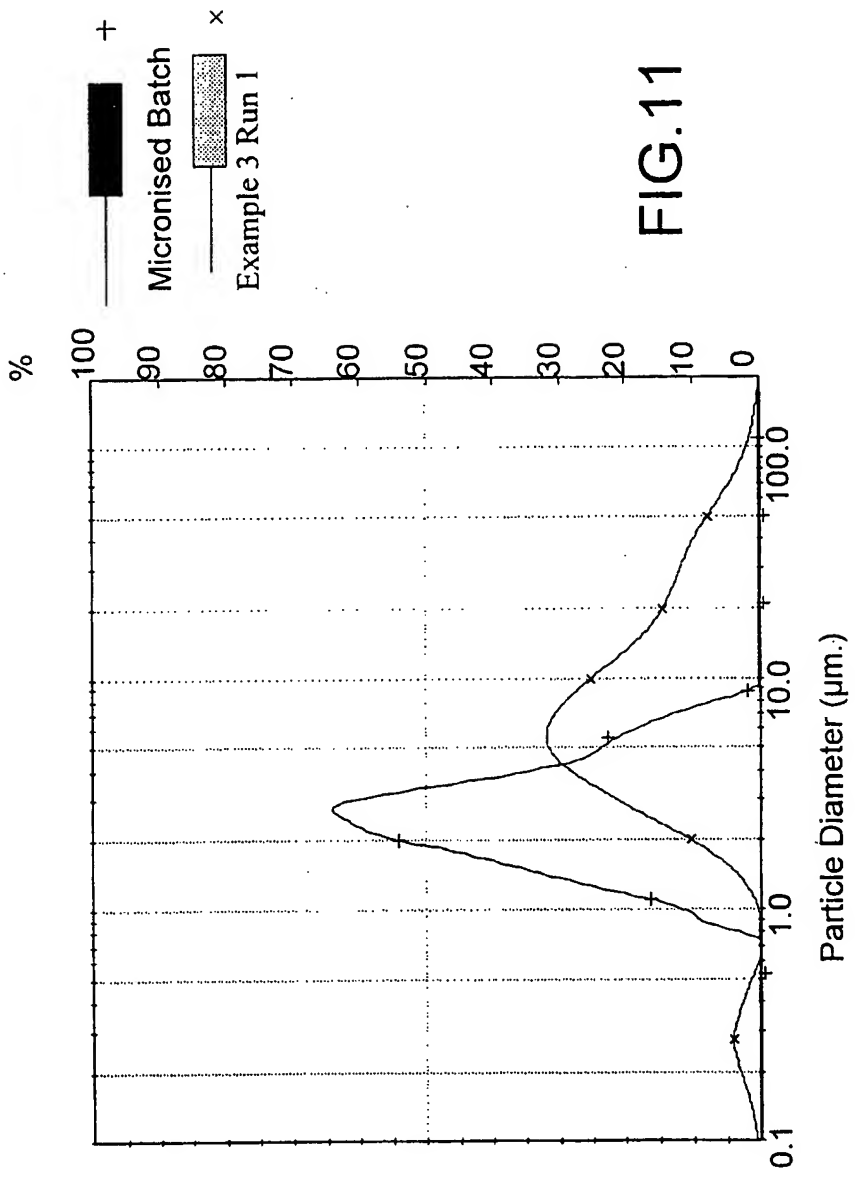

+
Micronised Batch
×
Example 3 Run 1
%
100
90
80
70
60
50
40
30
20
10
0
100.0
10.0
1.0
0.1
Particle Diameter (µm.)

FIG.11

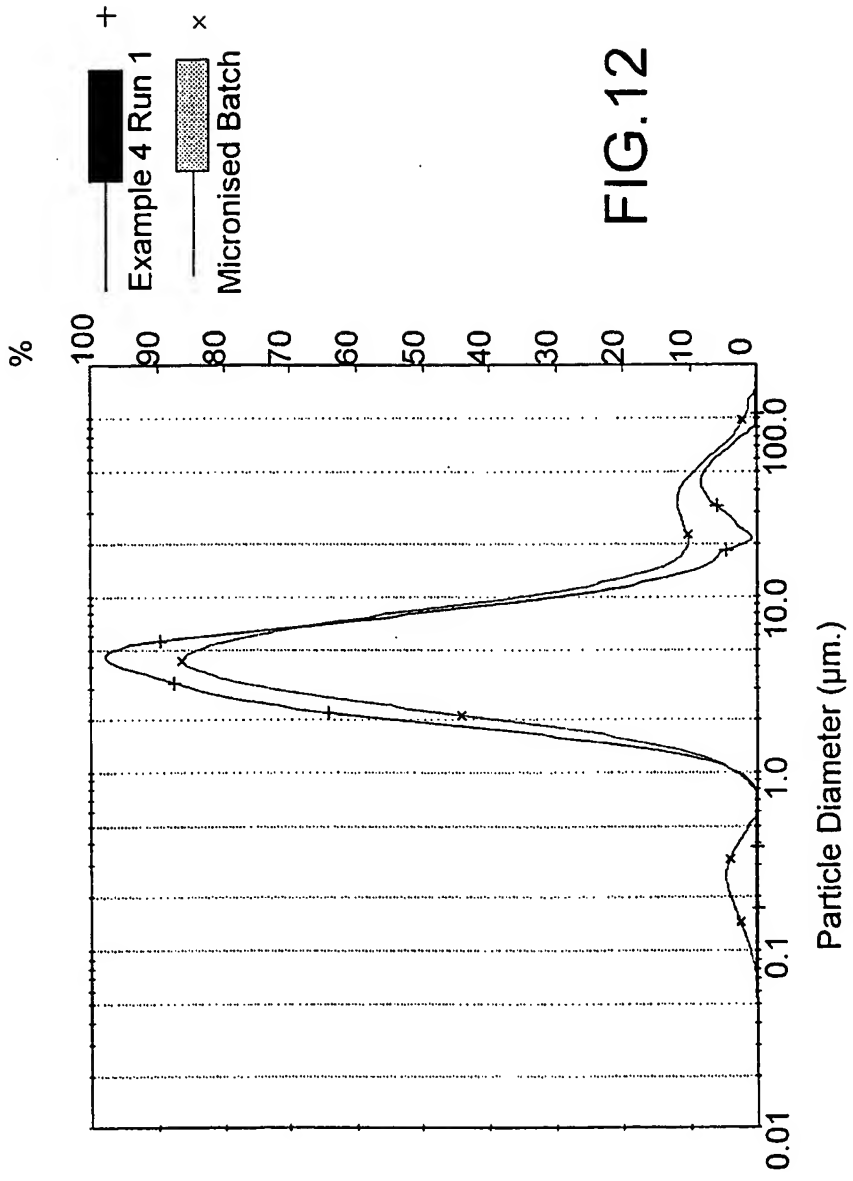

+
Example 4 Run 1
×
Micronised Batch
%
100
90
80
70
60
50
40
30
20
10
0
100.0
10.0
1.0
0.1
0.01
Particle Diameter (µm.)

FIG.12

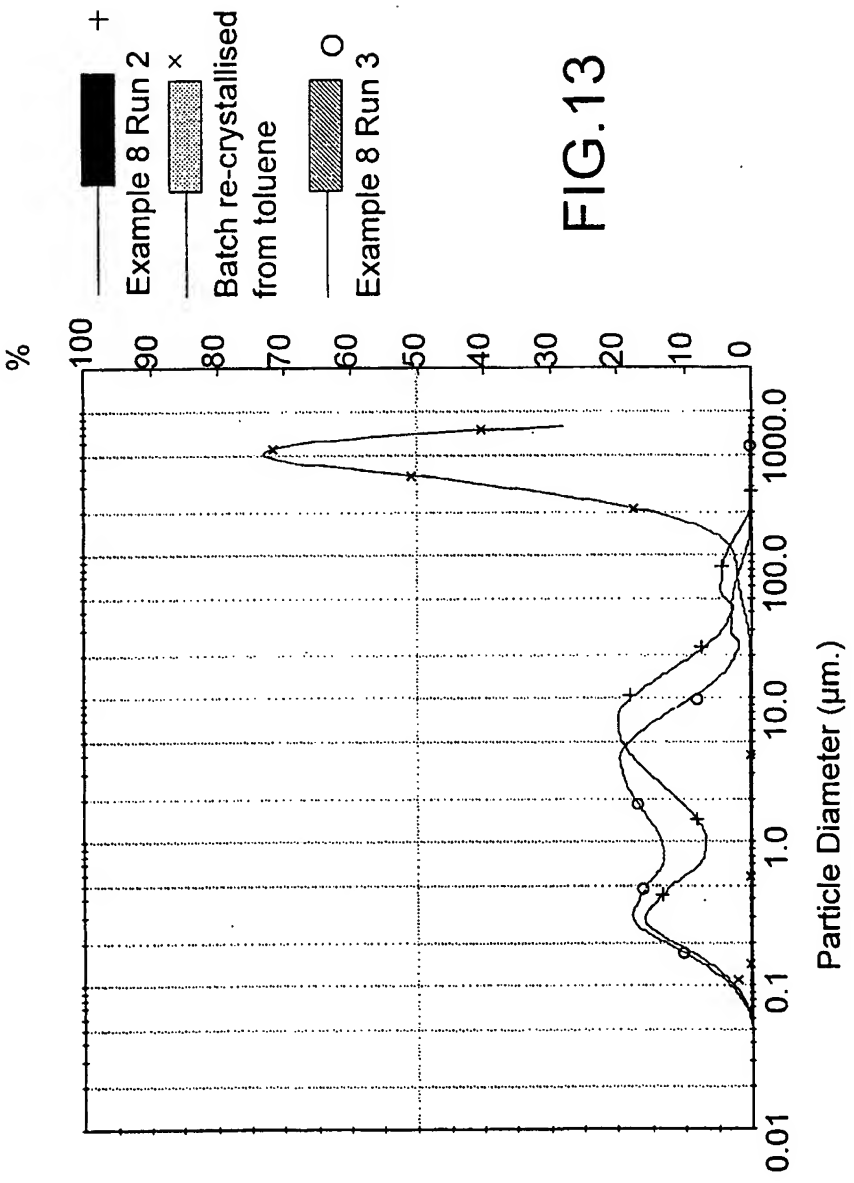

+
Example 8 Run 2
×
Batch re-crystallised from toluene
O
Example 8 Run 3
%
100
90
80
70
60
50
40
30
20
10
0
1000.0
100.0
10.0
1.0
0.1
0.01
Particle Diameter (µm.)

FIG.13

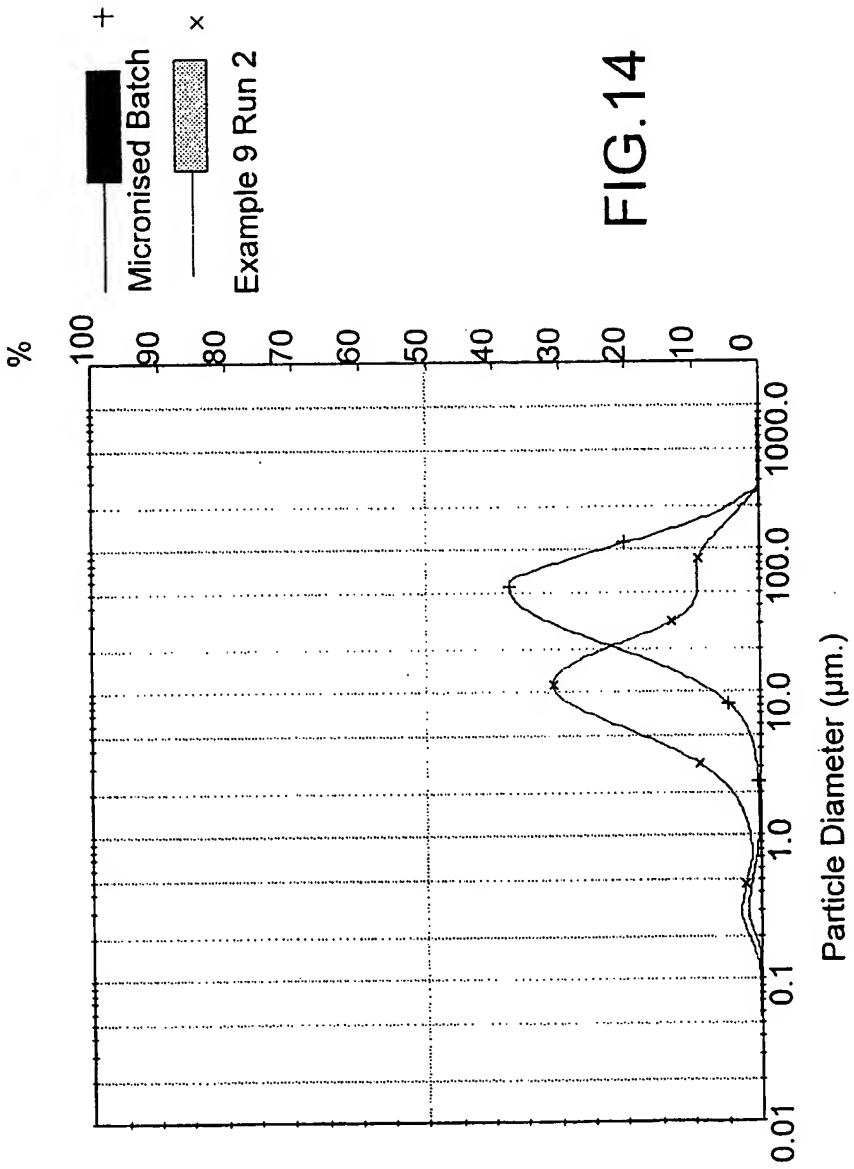

+
Micronised Batch
×
Example 9 Run 2
%
100
90
80
70
60
50
40
30
20
10
0
1000.0
100.0
10.0
1.0
0.1
0.01
Particle Diameter (µm.)

FIG.14

INTERNATIONAL SEARCH REPORT

Inter .onal Application No
PCT/GB 99/04368

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 B01D9/00 B01J19/10 A61K9/14

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 B01D B01J A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 96 32095 A (ASTRA AB ;JAKUPOVIC EDIB (SE); TROFAST JAN (SE)) 17 October 1996 (1996-10-17) claims ---	1-26
A	WO 90 03782 A (UPJOHN CO) 19 April 1990 (1990-04-19) claims; figure 1 ---	1-26
A	WO 98 33782 A (CLARKE WILLIAM ;CROCKER LOUIS S (US); MERCK & CO INC (US); KUKURA) 6 August 1998 (1998-08-06) claims; figures 1,2 ---	1-26
A	DE 25 04 347 A (DSO PHARMACHIM) 5 August 1976 (1976-08-05) the whole document -----	1-26

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
9 February 2000	16/02/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Persichini, C

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INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte .ional Application No
PCT/GB 99/04368

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